Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients

Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group

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Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospecti Study of the Infectious Diseases Working Party of European Bone Marrow Transplantation Group

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Abstract

Background

This intercontinental study aimed to study gram-negative rod (GNR) resistan hematopoietic stem cell transplantation (HSCT).

Methods

GNR bacteremias occurring during 6 months post-HSCT (February 2014–May were prospectively collected, and analyzed for rates and risk factors for resist fluoroquinolones, noncarbapenem anti-*Pseudomonas* β-lactams (noncarbapen carbapenems, and multidrug resistance.

Results

resistance were higher in auto-HSCT patients in centers providing vs not prov
fluoroquinolone prophylaxis ($P < .01$). Resistance rates were higher in southea
northwest Europe and similar in children and adults, excluding higher
fluoroquinolone- and β-lactam/β-lactamase inhibitor resistance rates in allo-
adults. Non-*Klebsiella* Enterobacteriaceae were rarely carbapenem resistant.
Multivariable analysis revealed resistance risk factors in allo-HSCT patients:
fluoroquinolone resistance: adult, prolonged neutropenia, breakthrough on
fluoroquinolones; noncarbapenem resistance: hospital-acquired infection,
breakthrough on noncarbapenems or other antibiotics (excluding fluoroquino
noncarbapenems, carbapenems), donor type; carbapenem resistance: breakth
on carbapenem, longer hospitalization, intensive care unit, previous other ant
therapy; multidrug resistance: longer hospitalization, breakthrough on β-lact
lactamase inhibitors, and carbapenems. Inappropriate empiric therapy and m
were significantly more common in infections caused by resistant bacteria.

Conclusions

Our data question the recommendation for fluoroquinolone prophylaxis and c
reassessment of local empiric antibiotic protocols. Knowledge of pathogen-sp
resistance enables early appropriate empiric therapy. Monitoring of resistance
crucial.

Keywords: antimicrobial resistance, gram-negative rods, hematopoietic stem cell
plantation, bacteremia

Topic: antibiotics, bacteremia, carbapenem, hematopoietic stem cell transplanta
adult, allopurinol, child, drug resistance, microbial, enterobacteriaceae,
fluoroquinolones, lactams, bacteria, pathogenic organism, gram-negative bacillus
vention, carbapenem resistance

Issue Section: Major Article

studies, mainly limited to single centers or countries, describe rates and ris
for specific resistant pathogens, such as extended-spectrum β-lactamase (
producing Enterobacteriaceae or multidrug-resistant (MDR) bacteria in pat
with cancer and HSCT recipients [10–13]. The majority, however, were perf
countries with high resistance rates in both the hospitalized and general
populations [12–14]. The risk of infection is influenced by local factors, am
prevalence of resistance, prophylactic practices, empiric treatment, and
antimicrobial stewardship. Only a handful of studies focus on children and
autologous HSCT (auto-HSCT) patients [12, 15, 16]. This study aimed to des
resistance rates and risk factors in GNR bacteremia in HSCT patients, based
intercontinental data.

METHODS

Study Design and Data Collection

This was a noninterventional prospective study. All patients in whom allog
HSCT (allo-HSCT) or auto-HSCT was performed during February 2014–Ma
the participating centers were included. Data on GNR bacteremia episodes t
occurred from the initiation of the conditioning regimen until 6 months aft
HSCT were reported, including pathogen and its antimicrobial susceptibilit
presence of risk factors, and mortality. This study was performed in accord
with the appropriate regulations in the participating countries including ap
the ethical committees as required, and registered at ClinicalTrials.gov
(NTC02257931).

The primary endpoint was to determine the proportion of GNRs resistant to
of noncarbapenem anti-*Pseudomonas* β-lactams (noncarbapenems), includi

Microbiological Workup

Guidelines used to determine isolates' susceptibility were by the European Committee for Antimicrobial Susceptibility Testing in 41 (64.1%) laboratori Clinical and Laboratory Standards Institute in 19 (29.7%) laboratories, and 4 (6.2%) laboratories. Resistance to antibiotics was studied by in vitro sens tests in the local laboratories using disk diffusion in 46 of 64 (71.9%) and/c minimum inhibitory concentration determination in 60 of 64 (93.8%) cent Pathogens with intermediate susceptibility to antibiotics were considered r

Definitions

An MDR GNR was defined as bacteria resistant to ≥1 agent in ≥3 of the follo categories: (1) broad-spectrum cephalosporins (ceftazidime or cefepime); (*Pseudomonas* βL/βLIs; (3) carbapenems; (4) aminoglycosides; (5) fluoroquin All *Stenotrophomonas maltophilia* strains were considered MDR. Extensively resistant (XDR) bacteria defined if checked for susceptibility to all relevant antimicrobials and found nonsusceptible to ≥1 agent in all but ≤2 categories Infections occurring >48 hours since the hospitalization were considered h acquired.

Neutropenia was defined as an absolute neutrophil count <500 cells/μL.

Breakthrough bacteremia was defined as bacteremia developing during ant treatment (including fluoroquinolone prophylaxis) provided for ≥48 hours obtaining the blood culture.

Geographic regions [4] included Northwest (Austria, Belgium, Denmark, Fi France, Germany, Netherlands, Sweden, Switzerland, United Kingdom); So

The incidence of resistance was computed as a percentage, the denominato
the number of GNR pathogens and the numerator being the number of path
classified as "resistant." Early mortality was computed as a percentage of d
occurred within 7 days after bacteremia on the episodes with a follow-up a
at the same time.

The relationship between resistance and the following risk factors was inve

- Background: sex, age at HSCT, underlying disease, myeloablative conditi
  fluoroquinolone prophylaxis.

- At the time of bacteremia: time since HSCT, duration of neutropenia, neu
  recovery, duration of hospitalization, hospital-acquired infection, breakt
  bacteremia, graft-vs-host disease (GVHD), acute GVHD grade II–IV, ven
  occlusive disease.

- Before bacteremia, within 1 month: urinary catheter, ≥2 weeks of steroid
  other immunosuppressive treatment; within 3 months: any hospitalizati
  hospitalization in the intensive care unit (ICU), any bacteremia, previous
  antibiotic therapy, and number of antibiotic classes.

Differences between groups were tested using linear or logistic regression m
using the generalized estimating equation method to take into account the
dependence of observations nested by patient and center [18]. The same mo
were used to study all relationships between resistance and characteristics
prognostic factors. Variables showing significance from the univariate mod
entered a multivariable model. The results obtained from these analyses are
considered as exploratory and hypothesis-generating.

A *P* value <.05 was considered statistically significant. All *P* values are 2 sid
the analyses were performed using the statistical software SAS version 9.4

Sixty-five HSCT centers from 25 countries reported data on 655 GNR episo
591 patients (1.1 episodes [range, 1–4] per patient) (Supplementary Table 1)
Characteristics of the background patients and episodes are presented in Ta
and 2. Median time to develop GNR bacteremia was 8 (range, −15 to 183) da
HSCT. Fluoroquinolone prophylaxis was provided in 34 of 45 (75.6%) allo-
22 of 49 (44.9%) auto-HSCT adult centers, and in 6 of 24 (25.0%) allo-HS
of 23 (8.7%) auto-HSCT pediatric centers.

Table 1.

Patient Characteristics (N = 591)

Characteristic	No. (%)
Age, y, median (range)	50.9 (0.3–7
Children (<18 y)	79 (13.4)
Male sex	357 (60.4)
Underlying disease	
Acute leukemia	212 (35.9)
Lymphoma	148 (25.0)
Plasma cell disorders	109 (18.4)
Myelodysplastic/myeloproliferative syndromes	54 (9.1)
Chronic leukemia	8 (1.4)
Solid tumor	12 (2.0)

Unrelated	175 (48.9)
Matched related	114 (31.8)
Mismatched related	69 (19.3)
Stem cell source	
Peripheral blood	451 (76.4)
Bone marrow	101 (17.1)
Both bone marrow and peripheral blood	10 (1.7)
Umbilical cord blood	28 (4.7)
Conditioning (allogeneic HSCT)	
Myeloablative	241 (68.1)
Nonmyeloablative	113 (31.9)
Karnofsky score, median (range)	90 (0–100)
Disease status after HSCT	
Continued complete remission	317 (75.1)
Never in complete remission	79 (18.7)
Partial remission/stable disease	26 (6.2)
Graft-vs-host disease prophylaxis before bacteremia (allogeneic HSCT)	
Total provided	339

Graft manipulation ex vivo (including T-cell depletion)	31 (6.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil.

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Table 2.

Episode Characteristics

Characteristic	Transplant Type		Total (N = 655)
	Allogeneic (n = 414)	Autologous (n = 241)	
Neutropenia at the time of episode <500 cells/µL	296 (71.5)	199 (82.9)	495 (75.7)
Neutropenia at the time of episode <100 cells/µL	259 (73.4)	175 (77.8)	434 (75.1)
Duration of neutropenia <500 cells/µL, d, median (range)	7 (1–246)	2.5 (1–124)	5 (1–246)
Duration of neutropenia <500 cells/µL <7 d, median (range)	153 (37.0)	189 (78.8)	342 (52.3)
Duration of neutropenia <100 cells/µL, d, median (range)	5 (1–80)	2 (1–28)	3 (1–80)
Duration of neutropenia <100 cells/µL <7 d	176 (49.9)	171 (76.0)	347 (60.0)
Absolute neutrophil count recovered before bacteremia	147 (39.9)	24 (10.8)	171 (28.9)

Hospital-acquired bacteremia	355 (86.8)	215 (90.7)	570 (88.2)
Previous ICU hospitalization	28 (6.9)	4 (1.7)	32 (4.9)
Bacteremia developed during hospitalization in the ICU	17 (4.2)	0 (0.0)	17 (2.6)
Breakthrough bacteremia	303 (73.4)	98 (40.7)	401 (61.3)
Cephalosporins[a]	30 (7.3)	8 (3.3)	38 (5.8)
Anti-*Pseudomonas* βL/βLIs	65 (15.7)	16 (6.6)	81 (12.4)
Carbapenems[b]	54 (13.1)	7 (2.9)	61 (9.3)
Any β-lactam[c]	159 (38.5)	36 (14.9)	195 (29.8)
Fluoroquinolones	118 (28.6)	50 (20.7)	168 (25.7)
Aminoglycosides	22 (5.3)	5 (2.1)	27 (4.1)
Others[d]	79 (19.1)	13 (5.4)	92 (14.1)
Previous antibiotic therapy	309 (77.3)	104 (44.4)	413 (65.1)
Cephalosporins[a]	46 (11.5)	8 (3.4)	54

			(37.9)
Fluoroquinolones	121 (30.3)	45 (19.2)	166 (26.2)
Aminoglycosides	30 (7.5)	5 (2.1)	35 (5.5)
Others[d]	101 (25.3)	12 (5.1)	113 (17.8)
No. of antibiotic classes of previous antibiotic therapy[e]			
1 antibiotic class	86 (21.4)	36 (15.3)	122 (19.2)
2 classes	73 (18.2)	24 (10.2)	97 (15.2)
≥3 antibiotic categories	131 (32.6)	18 (7.7)	149 (23.4)
GVHD at the time of bacteremia (% of all allo-HSCT)	71 (17.3)		
Acute GVHD at the time of bacteremia (% of all allo-HSCT)	62 (15.1)		
Grade II–IV of acute GVHD before bacteremia (% of all allo-HSCT)	12 (4.5)		
Chronic GVHD (% of all allo-HSCT)	9 (2)		
Veno-occlusive disease at the time of bacteremia	12 (2.9)	3 (1.3)	15 (2.3)

Recent steroid treatment	142 (34.5)	53 (22.3)	195 (30.0)
Time since HSCT, d, median (range)	11 (–15 to 183)	7 (–8 to 177)	8 (–15 to 183)
Central line infection	138 (38.4)	73 (32.3)	211 (36.1)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: allo, allogeneic; auto, autologous; βL/βLI, β-lactam/β-lactamase inhibitor; GVHD, g
host disease; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

[a] Cephalosporins: ceftazidime, cefepime, ceftriaxone, cefotaxime, cefuroxime, cefazolin.

[b] Carbapenems: meropenem, imipenem, ertapenem, doripenem.

[c] Any β-lactam: either cephalosporin, anti-*Pseudomonas* βL/βLI, carbapenem, or any other β-la
antibiotic.

[d] Others: any antibiotics, excluding any β-lactam, fluoroquinolones, aminoglycosides, and prop
use of trimethoprim-sulfamethoxazole or dapsone.

[e] Previous antibiotic exposure to the following antibiotic classes was reported: (a) any cephalos
anti-*Pseudomonas* βL/βLIs; (c) carbapenems (meropenem, imipenem, ertapenem, doripenem); (d
fluoroquinolones (either treatment and prophylaxis); (e) aminoglycosides; (f) macrolides; (g) anti
positives (glycopeptides, linezolid, daptomycin); (h) antianaerobes (metronidazole, clindamycin)
(j) tigecycline; (k) aztreonam; (l) other antibiotics.

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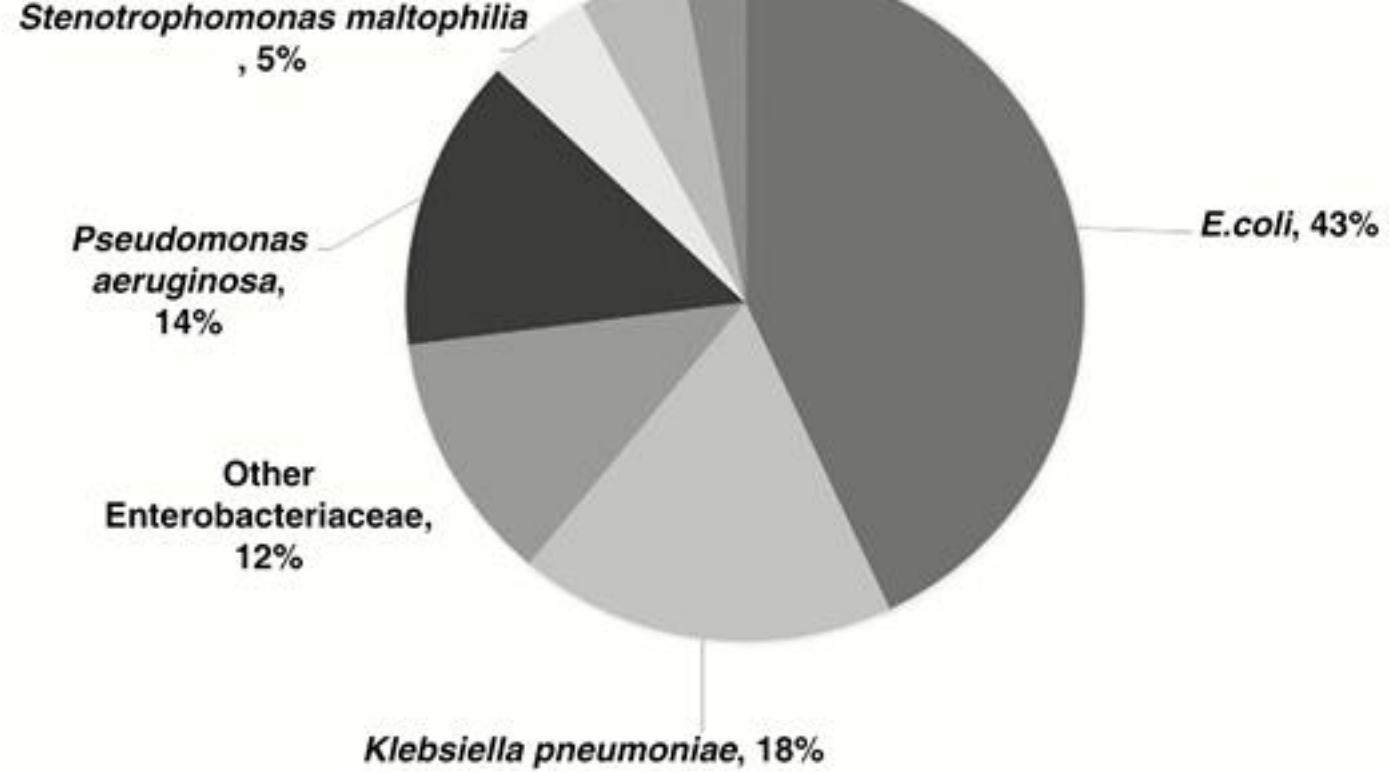
Microbiological Results

Seven hundred four GNRs included Enterobacteriaceae (514 [73%]),



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Distribution of gram-negative pathogens. Other Enterobacteriaceae include *Enterobacter* spp (n = *Klebsiella* spp (n = 24), *Citrobacter* spp (n = 12), *Serratia* spp (n = 6), *Proteus* spp (n = 3), *Raoultella* Other nonfermentative rods include *Acinetobacter* spp (n = 17), 1 each of *Sphingomonas paucimo* *Shewanella putrefaciens*, *Sphingobacterium multivorum*, *Comamonas testosterone*, *Ochrobactrum* *Ralstonia pickettii*, *Paracoccus yeei*, *Achromobacter xylosoxidans*. Other gram-negative rods includ *Capnocytophaga* spp (n = 8), *Moraxella* spp (n = 4), *Aeromonas* spp (n = 3), *Campylobacter* spp (n = *Rhizobium radiobacter* (n = 2), and 1 each of *Salmonella enteritidis*, *Haemophilus influenzae*, *Burkh* *cepacia*, *Elizabethkingia meningoseptica.*

Resistance Rates

Half of GNRs were resistant to fluoroquinolones and to noncarbapenems, 18 were carbapenem resistant, and 35.2% were MDR (Table 3). One of 73 (1.4% *Pseudomonas aeruginosa* and 4 of 14 (28.6%) *Acinetobacter* species were XDR Resistance rates to other antibiotics are presented in Table 3.

Table 3.

						Adu
Primary endpoints						
Fluoroquinolone	325/645 (50.4)	227/408 (55.6)*	98/237 (41.4)*	205/326 (62.9)**	22/82 (26.8)**	95/2 (41.1
Noncarbapenem β-lactam	322/632 (50.9)	241/407 (59.2)*	81/225 (36.0)*	199/322 (61.8)	42/85 (49.4)	78/2 (36.4
Carbapenem	127/688 (18.5)	105/443 (23.7)*	22/245 (8.9)*	80/349 (22.9)	25/94 (26.6)	20/2 (8.6)
Multidrug resistant	236/671 (35.2)	187/428 (43.7)*	49/243 (20.2)*	149/334 (44.6)	38/94 (40.4)	46/2 (19.9
Secondary endpoints						
Anti-*Pseudomonas* cephalosporin	255/656 (38.9)	199/416 (47.8)	56/240 (23.3)	160/332 (48.2)	39/84 (46.4)	55/2 (24.0
Anti-*Pseudomonas* βL/βLI	230/627 (36.7)	177/399 (44.4)	53/228 (23.2)	146/310 (47.1)***	31/89 (34.8)***	51/2 (23.5
Aminoglycoside	216/662 (32.6)	162/422 (38.4)	54/240 (22.5)	135/335 (40.3)	27/87 (31.0)	51/2 (22.4
Colistin	22/358 (6.1)	18/250 (7.2)	4/108 (3.7)	12/205 (5.9)	6/45 (13.3)	4/10 (3.9)
Tigecycline	15/182 (8.2)	12/124 (9.7)	3/58 (5.2)	10/109 (9.2)	2/15 (13.3)	3/58 (5.2)

Data are presented as no./No. (%). The following differences were significant: the resistance rates
fluoroquinolones, noncarbapenems, carbapenems, and multidrug resistance were significantly h

There was no strong correlation between the rates of GNR bacteremia and r to noncarbapenems and carbapenems per country; and no correlation betw fluoroquinolone resistance and bacteremia rate per center (Supplementary 1*A*–*C*).

Resistance Rates According to Pathogens

Fluoroquinolone resistance was significantly more frequent among Enterobacteriaceae (57.2% vs 30.7%; $P < .0001$); carbapenem resistance (50 8.4%; $P < .0001$), and multidrug resistance (46.6% vs 31.9%; $P = .001$) in nonfermentative rods (Table 4).

Table 4.

Resistance Rates According to Pathogens

Pathogens	Resistance to			
	Fluoro-quinolones	Noncarbapenem β-Lactams	Carbapenem	Multidrug Resistant
Escherichia coli	185/283 (65.4)	140/281 (49.8)	7/301 (2.3)	81/290 (27.9)
Klebsiella pneumoniae	71/111 (63.9)	79/118 (66.9)	31/124 (25.0)	63/121 (52.1)
Enterobacter spp	8/39 (20.5)	19/39 (48.7)	3/41 (7.3)	9/39 (23.1)
Other Enterobacteriaceae	7/41 (17.1)	9/43 (20.9)	2/45 (4.4)	5/44 (11.4)

Stenotrophomonas maltophilia	6/22 (27.3)	14/16 (87.5)	34/34 (100)	34/34 (100)
Other nonfermentative rods	4/22 (18.2)	13/20 (65.0)	5/21 (23.8)	7/22 (31.8)
Total nonfermentative rods	46/150 (30.7)[a]	68/138 (49.3)	82/161 (50.9)[a]	76/163 (46.6)[b]

Data are presented as no./No. (%).

[a] Significant differences between Enterobacteriaceae and nonfermentative rods ($P < .0001$).

[b] Significant differences between Enterobacteriaceae and nonfermentative rods ($P = .001$).

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Six of 31 (19%) *S. maltophilia* isolates were resistant to trimethoprim-sulfamethoxazole.

One-third of noncarbapenem-resistant, and half of MDR pathogens, were carbapenem resistant (Supplementary Table 2). Six of 33 (18.2%) carbapene resistant *P. aeruginosa* isolates were susceptible to both cephalosporins and (Supplementary Table 3); 1 of 29 (3.5%) was colistin resistant.

Among carbapenem-resistant Enterobacteriaceae, 15 of 41 (36.6%) were re amikacin, 16 of 41 (39.0%) to gentamicin, 4 of 41 (9.8%) to both aminoglyc 32 of 40 (78%) to fluoroquinolones, 5 of 17 (29.4%) to tigecycline, and 6 of (18.2%) to colistin.

Resistance Rate According to Hematopoietic Stem Cell Transplantatio

HSCT patients (Supplementary Tables 4 and 5).

Resistance Rate in Children Versus Adults

Similar resistance rates were observed in children and adults. Only the resis
rate to fluoroquinolones and βL/βLIs was significantly higher in adults com
with children following allo-HSCT ($P < .0001$ and $P = .048$, respectively) (Ta
the difference was significant in southeast countries only.

Geographical Distribution of Resistance Rates

There was a wide distribution in the resistance rates between countries
(Supplementary Table 6). Resistance rates were more frequent in the south
northwest European region: for noncarbapenems (266/481 [55.3%] vs 32/11
[27.6%], $P < .0001$); fluoroquinolones (270/496 [54.4%] vs 44/121 [36.4%];
.002); carbapenems (109/526 [20.7%] vs 6/123 [4.9%]; $P < .0001$); and mult
resistance (201/514 [39.1%] vs 16/118 [13.6%]; $P < .0001$).

Risk Factors for Resistance

Univariate analysis of risk factors for resistant GNRs in allo-HSCT and auto
recipients is presented in Supplementary Tables 4 and 5. Multivariable anal
possible in allo-HSCT patients only (Table 5), as rate of resistance was low
HSCT patients.

Table 5.

Multivariate Analysis of Risk Factors for Resistance in Gram-Negative Rods in Allogeneic Transplan

Risk Factor	Fluoroquinolone-Resistant GNRs	Noncarbapenem β-Lactam-	Carbapenem-Resistant GNRs	Mu Re

Breakthrough bacteremia on fluoroquinolones	7.26 (3.84–13.72)	<.0001		NS		NS	
Age (adults)	3.87 (2.07–7.25)	<.0001		NS		NS	
Hospital-acquired infection		NS	2.09 (1.08–4.03)	.029		NS	
Breakthrough bacteremia on βL/βLI		NS	2.45 (1.14–5.23)	.02		NS	2.3 (1. 4.4
Breakthrough bacteremia on cephalosporins		NS	6.36 (1.68–24.07)	.01		NS	
Previous antibiotic therapy with other antibiotics[a]		NS	2.59 (1.30–5.15)	.007	2.07 (1.15–3.73)	.016	
Longer duration of current hospitalization before episode		NS		NS	1.01 (1.00–1.02)	.041	1.0 (1. 1.0
Current bacteremia developed during hospitalization in the ICU		NS		NS	3.92 (1.18–3.03)	.026	
Breakthrough		NS		NS	9.08	<.0001	3.4

unrelated donor	4.35)

Abbreviation: βL/βLI, anti-*Pseudomonas* β-lactam β-lactamase inhibitor; CI, confidence interval; G negative rod; ICU, intensive care unit; NS, not significant; OR, odds ratio.

[a] Other antibiotics: any antibiotic therapy excluding β-lactams, fluoroquinolones, aminoglycosi

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To study the association between fluoroquinolone prophylaxis and resistan compared resistance rates in GNRs cultured during the period when prophy provided (in neutropenic patients without empiric or targeted antibiotics th in centers that do and do not provide prophylaxis.

The rate of fluoroquinolone-resistant GNRs was higher in centers providing prophylaxis (79% vs 50%, $P = .001$ in allo-HSCT; 74% vs 25%, $P < .001$ in a HSCT). The rate of noncarbapenem-resistant (36% vs 13%; $P = .002$) and M vs 8%; $P < .001$) bacteria was higher in auto-HSCT patients in centers provi prophylaxis (Supplementary Table 7).

Outcome

The 7-day mortality was 38 of 589 (6.5%). The mortality according to resis pattern was 9% vs 2% ($P = .002$) in episodes caused by noncarbapenem res sensitive GNRs; 18% vs 4% ($P < .001$) in those carbapenem resistant vs sens and 11% vs 4% ($P = .002$) in MDR vs non-MDR. Inappropriate empiric thera provided for 124 of 586 (21.2%) GNRs; being 101 of 270 (37.4%) for noncarb resistant vs 12 of 274 (4.4%) noncarbapenem susceptible bacteria; 62 of 97 for carbapenem resistant vs 61 of 481 (12.7%) carbapenem susceptible; and (46.2%) for MDR vs 30 of 368 (8.1%) non-MDR GNRs ($P < .001$ for all).

resistance.

The emerging resistance challenges antibacterial prophylaxis policy and complicates empiric and targeted treatment choices. Benefit of fluoroquino prophylaxis was demonstrated in a country with a baseline resistance of approximately 20% in GNRs from the community and medical departments In our study, 39% of GNRs causing community-acquired infections in allo- and 63% in auto-HSCT were fluoroquinolone resistant (Supplementary Tab 5). High rates of fluoroquinolone resistance may be the price to pay for low of bacteremia in centers providing prophylaxis. We could not, however, den correlation between the rates of bacteremia and fluoroquinolone resistance (Supplementary Figure 1*A*). Doubts regarding the benefits of fluoroquinolon prophylaxis are accompanied by concern about increased rates of resistance antibiotics following exposure to fluoroquinolones. No association between fluoroquinolone prophylaxis and the increase in MDR bacteria was shown i meta-analysis of studies published up to 2005 [21]. Later published studies however, correlated exposure to fluoroquinolones with increase in infection resulting from fluoroquinolone-resistant, ESBL-producing, carbapenem-re and MDR pathogens [14, 22, 23]. In our study, in auto-HSCT patients, treat centers providing fluoroquinolone prophylaxis, breakthrough on fluoroquin and previous exposure to fluoroquinolones (Supplementary Tables 5 and 7) associated with resistance to noncarbapenems and MDR. The risk could, ho be influenced by other factors, as outpatient vs inpatient transplantation se which were not reported in our study. The benefits and potential risks of fluoroquinolone prophylaxis must be carefully assessed, especially in cente high fluoroquinolone resistance rates among GNRs [24].

Empiric treatment with noncarbapenem β-lactams, or even carbapenems [be inappropriate in centers with high resistance rates to these antibiotics a to increased mortality [2, 13]. In our study, approximately 40% of commun

for empiric therapy are tricky because of significant geographical variations
Practical decisions on empiric therapy must be based on continuously upda
concerning local resistance patterns and bacteremia rates [26]. We are thus
to recommend the specific resistance rate threshold that indicates change i
empiric therapy protocol as our study was not designed to answer this ques
While the proportion of resistant bacteria was high in some centers, its imp
patient outcome can be low if GNR bacteremia is rare (Supplementary Figu
and 1*C*).

Resistance to multiple antibiotics complicates the targeted therapy choice.
Susceptibility to tigecycline, polymyxins, fosfomycin, and aminoglycosides
promptly reported in the centers with carbapenem-resistant infections, as
bacteria were resistant to these last-resort antibiotics in our and other stud
27]. Eighteen percent of carbapenem-resistant *P. aeruginosa* was susceptibl
cephalosporins and βL/βLIs in our study and, in contrast to carbapenem-re
Enterobacteriaceae, can be treated with these agents, especially administere
high-dose prolonged infusion [28].

Knowledge of pathogen-specific resistance patterns can help direct approp
empiric therapy following rapid bacterial identification by matrix-assisted
desorption/ionization–time of flight (MALDI-TOF), prior to susceptibility r
Carbapenem monotherapy should be appropriate on identification of non–*K*
pneumoniae Enterobacteriaceae, which are usually carbapenem susceptible.
carbapenem/colistin with or without aminoglycoside combination should, h
be considered for *K. pneumoniae* or *Acinetobacter* pending susceptibility resu
significant proportion of them are carbapenem resistant. Streamlining of a
therapy, of course, should be performed when susceptibilities are available.

Data on resistance rates in post-HSCT children are scarce [12, 16, 29]. Surp
resistance rates were mostly similar in children and in adults in our study.

Information about resistance rates and risk factors in auto-HSCT patients i
and mainly concerns fluoroquinolones [15, 30], as bacteremia is relatively l
frequent in auto-HSCT patients [31]. Certain factors predisposing to resista
infections—such as breakthrough bacteremia and prolonged neutropenia—
frequent in auto-HSCT vs allo-HSCT patients (Table 2). Although total resi
rates were higher in allo-HSCT patients, resistance rates in community-ac
infections were similar. These data reinforce the importance of monitoring
antibiotic susceptibilities in auto-HSCT patients.

Several studies reported risk factors for cephalosporin-resistant, ESBL-pro
or MDR bacteria in cancer and HSCT patients [10, 12, 13, 16, 22, 29, 32]. Onl
handful describe risk factors for carbapenem-resistant infections in popula
involving but not limited to transplant patients, mainly for *K. pneumoniae*. I
from other studies, we found that breakthrough on noncarbapenems does n
predispose to carbapenem resistance in allo-HSCT patients [8, 14]. Noncarb
β-lactams and carbapenems are both recommended for empiric treatment i
neutropenic patients [25], half of whom have neither microbiological nor cl
infection. Limitation of carbapenem treatment, de-escalation to a narrower
spectrum regimen following culture results, and shortening treatment dura
recommended by European Conference on Infections in Leukaemia guidelin
slow development of carbapenem resistance without increasing mortality [

Geographical differences in resistance rates are striking. In certain countrie
found higher resistance rates than those previously reported in the literatu
France, for example, 34.4% of GNRs were noncarbapenem resistant, compa
4% third-generation cephalosporin resistance among Enterobacteriaceae c
in hematological malignancies and post-HSCT patients during 2003–2010,
may be explained by increased resistance rates over time [5]. Information a
resistance rates in each country may, of course, be skewed by local epidemi

significantly higher resistance rates in southeast as compared with northw
Europe. This correlates with lower rates of antimicrobial resistance among
general population [36], which is probably explained by lower consumption
systemic antibacterials in the community, as well as in veterinary medicine
northwest Europe [37, 38].

The multidrug resistance rate (~30%) among Enterobac teriaceae and *P. aer*
in our study was within that reported in cancer and HSCT patients [11–13, 3
rate of cotrimoxazole resistance among *S. maltophilia*, the drug of choice for
MDR pathogen, was higher in our study (19%) compared to 4%–10% in oth
studies [5, 29]. Susceptibility of *Acinetobacter* species in cancer and transpla
patients has been infrequently studied [5, 29, 39]; XDR *Acinetobacter* infecti
not previously reported. In our study, a third of *Acinetobacter* species were X

We demonstrated higher mortality rates in infections caused by resistant ba
similar to other studies [8, 12]. Analysis of mortality risk factors is beyond t
of this manuscript.

Our study has limitations. GNR resistance rates and patterns in our study ar
influenced by the epidemiology of countries with more participating center
Antimicrobial susceptibility data were incomplete for some GNRs. Resistanc
to certain agents, such as tigecycline, could be overestimated, as susceptibi
likely checked in bacteria resistant to other treatment options, or reflecting
epidemiology. We could, however, demonstrate resistance rates to salvage
treatments among their main targets, harder-to-treat pathogens. We did n
important risk factors for resistance: history of recent residency in another
(information unavailable) and prior colonization with resistant GNRs (not a
participating centers performed colonization screening).

The study has important strengths. It is the first intercontinental prospecti

studies, we analyze risk factors for different resistance patterns and pathog
rather than focusing on specific bacteria or mechanisms.

In conclusion, the problem of antibiotic resistance is worrying in all HSCT p
including subgroups of children and auto-HSCT recipients. It is associated
inappropriate empiric therapy and increased mortality. Benefits of fluoroqu
prophylaxis and the approach to empiric therapy should be reassessed and
in continuous monitoring of the local bacteremia rates and susceptibility da
infecting pathogens. Knowledge of pathogen-specific resistances enables e
appropriate empiric therapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online.
Consisting of data provided by the authors to benefit the reader, the posted
materials are not copyedited and are the sole responsibility of the authors,
questions or comments should be addressed to the corresponding author.

Notes

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